AMENDMENTS TO THE CLAIMS

Please amend claims 1, 2, 4-8, 18, and 20 as indicated below. Please cancel claim 3, and add new claims 21-28. Pursuant to 37 C.F.R. §1.121, as amended, a detailed listing of all claims that are, or were, in the application, is listed below. The current status of all claims is indicated in parentheses after the claim number:

Claim 1 (currently amended): A method of treating a patient at risk of loss of cardiac function by cardiac ischemia, comprising

(a) imaging the patient's heart, or a portion thereof, to identify (i) an underperfused region of cardiac muscle, (ii) a source of oxygenated blood that is proximate a boundary of the underperfused region, and (iii) a target area that includes said underperfused-region boundary and a tissue expanse lying between said oxygenated blood supply and said boundary;

(b) at each of a plurality of sites throughout the target area, introducing a stimulus effective to stimulate angiogenesis in myocardial tissue and form a capillary network from the source of oxygenated blood to the underperfused region; and

(c) sustaining a demand for oxygen at the underperfused region for a period sufficient to covert the capillary network into an arterial network;

wherein said sustaining is accomplished by requiring the patient to undergo a regular exercise regime.

Claim 2 (currently amended): The method of claim 1, wherein step (a) includes monitoring blood flow in the heart by myocardial perfusion imaging by a method selected from ~~the group consisting of~~ (i) single-photon emission computed tomography (SPECT), (ii) positron-emission tomography (PET), (iii) echo-planar imaging, (iv) myocardial perfusion imaging by dynamic contrast MRI, ~~and~~ or (v) angiography.

Claim 3 (canceled).

Claim ~~4~~ 3 (currently amended): The method of claim 1, wherein said sustaining is further accomplished ~~to~~ by producing a slow-healing or repeated injury at or near said target-area sites.

Claim ~~5~~ 4 (currently amended): The method of claim 1, wherein the stimulus introduced in step (b) is a growth factor selected from ~~the group consisting of~~ fibroblast growth factor-I (FGF-1 or FGF-2), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor-I (IGF-1), ~~and~~ or combinations of two or more of these growth factors.

Claim ~~6~~ 5 (currently amended): The method of claim ~~5~~ 4, wherein the growth factor is introduced in the form of a recombinant protein carried in a pharmaceutically acceptable medium, and the growth factor is introduced by a method selected from ~~the group consisting of~~ (i) injecting the protein directly into myocardial tissue at said site, (ii) drawing the protein into myocardial tissue at said site by iontophoresis from a reservoir placed against the site, (iii) forming a channel in the myocardium at said site, and placing the protein into the channel, ~~and~~ or (iv) bombarding said site with a biolistic particle containing or coated with the protein.

Claim ~~7~~ 6 (currently amended): The method of claim ~~5~~ 4, wherein said growth factor is introduced ~~is~~ by a vector containing the coding sequence for the growth factor and a control region effective to promote transcription of said coding region in patient myocardial cells, and the vector is introduced by a method selected from ~~the group consisting of~~ (i) injecting the vector directly into myocardial tissue at said site, (ii) drawing the vector into myocardial tissue at said site by iontophoresis from a reservoir placed against the site, (iii) forming a channel in the myocardium at said site, and placing the vector into the channel, ~~and~~ or (iv) bombarding said site with a biolistic particle containing or coated with the vector.

Claim ~~8~~ 7 (currently amended): The method of claim ~~5~~ 4, wherein said growth factor is introduced in the form of a myocardial or cardiac myoblast cell which has been transformed with a gene encoding the growth factor, and the transformed cell is introduced by a method selected from ~~the group consisting of~~ (i) injecting the cell directly into myocardial tissue at said site, (ii) forming a channel in the myocardium at said site, and placing the cell into the channel, ~~and (iv)~~ or (iii) bombarding said site with a biolistic particle containing or coated with the cell.

Claim 8 (original): The method of claim 5, wherein step (b) is carried out so as to create a temporal gradient of growth factor availability in the target area, progressing from greater short-term availability near the source of oxygenated blood and more long-term availability near and in the boundary of the underperfused region.

Claim 10 (withdrawn): The method of claim 1, wherein the stimulus introduced into the target area in step (b) is an injury produced by a stimulus selected from the group consisting of a mechanical, laser, chemical, thermal, or ultrasonic injury.

Claim 11 (withdrawn): The method of claim 10, wherein the injury if produced by a mechanical cutting device effective to produce an annulus of injury about a core of healthy cells.

Claim 12 (withdrawn): The method of claim 10, wherein the stimulus is a mechanical stimulus produced by introducing into each of said sites, a wire device having a barbed segment, and the method further includes periodically moving the wire devices relative to the heart, to produce a prolonged angiogenic stimulus at said site.

Claim 13 (withdrawn): The method of claim 1, wherein the source of oxygenated blood is one in which arteries les than about 1 mm branch into surrounding arterioles, and in which the arterioles with inner lumen diameters between about 50-200 microns are plentiful, and said sites are spaced from one another at spacing of between 0.5 to 1 cm.

Claim 14 (withdrawn): The method of claim 1, wherein the underperfused region is in a myocardial region of either of the patient's ventricles, the source of oxygenated blood is the interior of the underperfused heart ventricle region, the target area includes the region of ventricle endocardium underlying the underperfused region, and said stimulus I s a mechanical injury produced by forming at selected target sites in the target area, elongate channels in the endocardium of the ventricle, where the depth and width of said channels, combined with the blood turbulence produced within the ventricle, is such as to minimize accumulation of blood clot material in the channels.

Claim 15 (withdrawn): The method of claim 14, wherein the chaneels have both width and depth dimetnsion between 1-5 mm.

Claim 16 (withdrawn): The method of claim 15, which further includes introducing an angiogenic growth factor into target-area sites between the underperfused region and adjacent portions of the inner ventricle wall.

Claim 17 (withdrawn): The method of claim 15, which further includes, the steps of

(c) imaging the heart to identify (i) as a second source of oxygenated blood, coronary arterioles in the epicardial region of the ventricle overlying the underperfused heart-ventricle region, (ii) as a second target area, the area between the second source of oxygenated blood supply and the underperfused region, and the adjacent boundary of the underperfused region; and

(d) introducing into the second target area, at selected sites therein, a stimulus effective to stimulate angiogenesis in the target area.

Claim ~~18~~ 9 (currently amended): A method of treating a patient at risk of loss of cardiac function by cardiac ischemia, comprising

(a) imaging the patient's heart, or a portion thereof, to identify (i) an underperfused region of cardiac muscle, (ii) a source of oxygenated blood that is proximate a boundary of the underperfused region, and (iii) a target area that includes said underperfused-region boundary and a tissue expanse lying between said oxygenated blood supply and said boundary;

(b) at each of a plurality of sites throughout the target area, introducing a stimulus effective to stimulate angiogenesis in myocardial tissue and form a capillary network from the source of oxygenated blood to the underperfused region;

~~The method of claim 1, which further includes the step of~~ (c) ~~following step (b),~~ equipping the patient with an exercise monitor that indicates the level and amount of heart exercise the patient achieves; and

(d) requiring the patient to achieve an amount and level of heart exercise effective to stimulate the conversion of capillary blush produced by said step (b) to arterioles in the target area.

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Claim ~~19~~ (original): The method of claim ~~18~~, wherein a pacemaker is used to exercise the patient's heart.

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Claim ~~20~~ (currently amended): The method of claim ~~10~~ 1, wherein the stimulus introduced into the target area is a combination of mechanical injury and chemical injury.

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Claim ~~21~~ (new): A method of treating a patient at risk of loss of cardiac function by cardiac ischemia, comprising

(a) imaging the patient's heart, or a portion thereof, to identify (i) an underperfused region of cardiac muscle, (ii) a source of oxygenated blood that is proximate a boundary of the underperfused region, and (iii) a target area that includes said underperfused-region boundary and a tissue expanse lying between said oxygenated blood supply and said boundary;

(b) at each of a plurality of sites throughout the target area, introducing a stimulus effective to stimulate angiogenesis in myocardial tissue and form a capillary network from the source of oxygenated blood to the underperfused region; and

(c) sustaining a demand for oxygen at the underperfused region for a period sufficient to covert the capillary network into an arterial network;

wherein:

the stimulus introduced in step (b) is a growth factor; and

the growth factor is introduced by a method selected from (i) drawing the growth factor into myocardial tissue at said site by iontophoresis from a reservoir placed against the site, (ii) forming a channel in the myocardium at said site, and placing the growth factor into the channel, or (iii) bombarding said site with a biolistic particle containing or coated with the growth factor.

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Claim ~~22~~ (new): The method of claim ~~21~~, wherein step (a) includes monitoring blood flow in the heart by myocardial perfusion imaging by a method selected from (i) single-photon emission computed tomography (SPECT), (ii) positron-emission tomography (PET), (iii) echo-planar imaging, (iv) myocardial perfusion imaging by dynamic contrast MRI, or (v) angiography.

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Claim ~~23~~ (new): The method of claim ~~21~~, wherein said sustaining is accomplished by producing a slow-healing or repeated injury at or near said target-area sites.

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Claim ~~24~~ (new): The method of claim ~~21~~, wherein the growth factor is introduced in the form of a recombinant protein carried in a pharmaceutically acceptable medium.

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Claim ~~25~~ (new): The method of claim ~~21~~, wherein said growth factor is introduced by a vector containing the coding sequence for the growth factor and a control region effective to promote transcription of said coding region in patient myocardial cells.

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Claim ~~26~~ (new): The method of claim ~~21~~, wherein said growth factor is introduced in the form of a myocardial or cardiac myoblast cell which has been transformed with a gene encoding the growth factor.

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Claim ~~27~~ (new): The method of claim ~~21~~, wherein the growth factor is selected from fibroblast growth factor-I (FGF-1 or FGF-2), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor-I (IGF-1), or combinations of two or more of these growth factors.

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Claim ~~28~~ (new): A method of treating a patient at risk of loss of cardiac function by cardiac ischemia, comprising

(a) imaging the patient's heart, or a portion thereof, to identify (i) an underperfused region of cardiac muscle, (ii) a source of oxygenated blood that is proximate a boundary of the underperfused region, and (iii) a target area that includes said underperfused-region boundary and a tissue expanse lying between said oxygenated blood supply and said boundary;

(b) at each of a plurality of sites throughout the target area, introducing a stimulus effective to stimulate angiogenesis in myocardial tissue and form a capillary network from the source of oxygenated blood to the underperfused region; and

(c) sustaining a demand for oxygen at the underperfused region for a period sufficient to covert the capillary network into an arterial network;

wherein:

the stimulus introduced in step (b) is a growth factor selected from fibroblast growth factor-I (FGF-1 or FGF-2), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor-I (IGF-1), or combinations of two or more of these growth factors; and

wherein step (b) is carried out so as to create a temporal gradient of growth factor availability in the target area, progressing from greater short-term availability near the source of oxygenated blood and more long-term availability near and in the boundary of the underperfused region.